Clinical Applications of Biologics in Eyecare COPE 75251-AS

Walt Whitley, OD, MBA, FAAO
Director of Professional Relations and Education
Virginia Eye Consultants
Regional Medical Director
Eyecare Partners, LLC

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Biologics: What Are They?

- FDA defines biological products as "a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins…composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells or tissues…isolated from a variety of natural sources – human, animal, or microorganism"
- Biologics are specialty bioengineered molecules produces in living systems

2

Biologics: Great So What Do They Do?

- *Used to diagnose, prevent, treat, and cure numerous diseases and medical conditions*
  - Therapeutic proteins (filgrastin)
  - Monoclonal antibodies (adalimumab)
  - Vaccines (tetanus)
- Most advance therapies available
  - 1st vs 2nd vs 3rd line treatments??
  - Fail first on other meds??

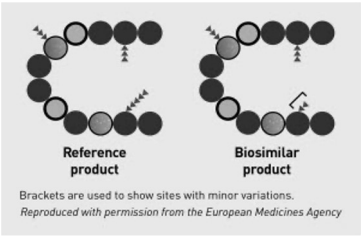
3

Biologics versus Chemical Drugs

- Small molecular drugs are composed of 20-100 atoms
- Small biologics – 200 to 3,000 atoms
- *Large biologics – 5,000 to 50,000 atoms*

4

Biologics vs Biosimilars vs Interchangeable



Brackets are used to show sites with minor variations.
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Source: https://www.fda.gov/drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm580419.htm

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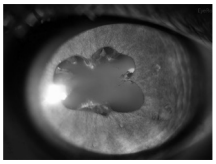
Applications in Eye Care

- Ocular surface disease
- Inflammatory disease
  - Uveitis
  - Scleritis/Episcleritis
- Oculoplastics
  - Cosmetic
  - Functional
- Retina
  - Age related macular degeneration
  - Diabetic retinopathy



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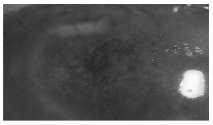
Current Uses for Topical Biologics for OSD

- Persistent epithelial defects
  - Neurotrophic keratopathy
  - Exposure keratopathy
- Recalcitrant dry eye
- Filamentary keratitis
- Corneal ulcers
- Herpetic keratitis
- Steven-Johnson's Syndrome
- Keratoneuralgia
- Recurrent corneal erosion
- Limbal stem cell deficiency



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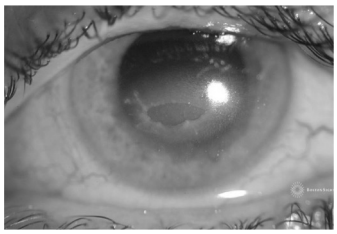
Neurotropic Keratitis Definition



- Degenerative corneal disease
- Damage to the trigeminal nerve (cranial nerve V)
- Loss of corneal sensation
- Breakdown of the corneal epithelium
- Impaired corneal healing
- Persistent epithelial defect → corneal ulceration → stromal melting and perforation

Hallmark: decreased sensation, decreased or no pain

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Neurotrophic Keratitis

- Rare/orphan disease (ORPHA137596)[1]
  - Affects ≤ 5 individuals in 10,000
- NK Prevalence difficult to determine[1,2]
  - Estimated to be < 1.6/10,000
  - Best data are based on extrapolation from the most common conditions associated with NK
    - Herpes simplex keratitis: 6% develop NK
    - Herpes zoster keratitis: 12.8% develop NK
    - Postsurgical nerve damage: 2.8% develop NK

1. Dua HS, et al. Prog Retinal Eye Res. 2018;66:107-131.
2. Saad S, et al. Ocular Surf. doi:10.1016/j.jtos.2019.11.008.

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Differential Diagnosis

- **Loss of corneal sensation = NK**
- **Neuropathic pain (corneal neuralgia, keratoneuralgia)**
  - Pain without stain
  - Pain in response to minimal or even no stimulus
- **Diseases with overlapping features of NK; can lead to NK if corneal sensation is affected[1,2]**
  - Dry eye disease
  - Contact lens-related disorders
  - Blepharitis
  - Exposure keratopathy
  - Stem cell deficiency
  - Topical drug toxicity
  - Mild chemical injury

1. Dua HS, et al. Prog Retinal Eye Res. 2018;66:107-131.
2. Sacchetti A, et al. Clinical Ophthalmology. 2014;8:571–579.

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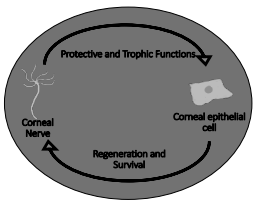
Corneal Innervation



- The cornea is the most sensitive and densely innervated tissue in the human body[1,2]
- Corneal innervation is essential. Corneal epithelial cells act in a mutually supportive relationship with corneal nerves[1-4]
  - Corneal nerves: maintain corneal integrity
    - Protective functions: blinking and tearing
    - Trophic support: neuropeptides (eg, substance P) promote epithelial cell proliferation, migration, adhesion
  - Epithelial cells: neurotrophic factors (neuronal extension and survival)
- Corneal nerve damage = loss of corneal sensation, epithelial breakdown, poor healing[1,2]

1. Shaha H. Clinical Ophthalmology. 2019:13:1973-1980.
2. Versura P, et al. Eye and Brain. 2018:10:37-45.
3. Dua HS, et al. Prog Retinal Eye Res. 2018;66:107-131.
4. Saad S, et al. Ocular Surf. doi:10.1016/j.jtos.2019.11.008.

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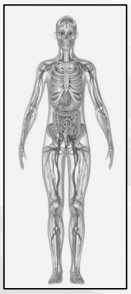
Etiology



INFECTIOUS[1,2]
- Herpes (simplex, zoster)
- Leprosy

IATROGENIC[1,2]
- Trauma to ciliary nerves by laser treatment and surgery
- Corneal incisions
- LASIK

SYSTEMIC DISEASE[1,2]
- Diabetes
- Multiple sclerosis
- Vitamin A deficiency

CORNEAL DYSTROPHIES[1,2]
- Lattice
- Granular

TOXIC[1,2]
- Chemical burns
- Carbon disulfide exposure
- Hydrogen sulfide exposure

TOPICAL MEDICATIONS[1,2]
- Anesthetics (abuse)
- Timolol
- Betaxolol
- Sulfacetamide
- Diclofenac sodium
- Ketorolac

MISC[2]
- CTL
- Increasing age
- Dark eye color
- Adie syndrome
- Limbal stem cell failure (chronic)

FIFTH-NERVE PALSY[1,2]
- Trigeminal neuralgia surgery
- Neoplasia (acoustic neuroma)
- Aneurysms
- Facial trauma
- Congenital
- Riley-Day syndrome
- Goldenhar-Gorlin syndrome
- Möbius syndrome
- Familial corneal hypesthesia

1. Dua, HS, et al. Prog Retinal Eye Res. 2018;66:107-131.
2. Medscape. Neurotrophic keratitis. https://emedicine.medscape.com/article/1194849-overview

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Case Ex.

- The 84 year old, AA female presents for 3-4 month DES check (no touch) and MMP-9 testing. Pt has a h/o DES and POAG mild OU. Pt states OS>OD has some itching. Pt states she has only been using her cyclosporine 0.05% and AT's. She never picked up fluoromethalone drops and is not using AT's ointment or a heat mask.

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- Ocular Hx:
  - Dry eye syndrome – 10+ yrs
  - Herpes stromal keratitis OS
    - Inactive – Last episode 2020
  - Anterior scleritis OS
    - Inactive
  - POAG - Mild OU
  - Pterygium sx OU
  - Phaco OU
  - Previous treatments
    - Amniotic membrane OS (2019, 2020)
    - Punctal cautery (2011) OU
- Med Hx:
  - NIDDM 15 yrs
  - Osteoarthritis
  - Hypothyroid
  - Seasonal allergies
- Meds:
  - Ceterizine
  - Lactulose
  - Levothyroxine

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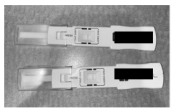
Clinical Exam

- Lids / Lashes – Clear and good position
- Conjunctiva – tr injection OU
- Cornea
  - OD 2+ Inf SPK
  - OS Dense SPK, 1+ K edema
- A/C – Deep and Quiet
- PCIOL OU
- IOP – 11 mmHg OU
- K Sensitivity – OD Normal OS Reduced



Anything else we should add???

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Corneal Sensation

- Greatest in the central cornea (elderly patients - more sensitive in the periphery)
- Drops rapidly as distance increases from the limbus
- Falls with increasing age
- Is not affected by iris color
- More sensitive in the temporal limbus than the inferior limbus
- Reduction has been reported in diabetes type 1 and type 2

Faulkner WJ, Varley GA. Corneal diagnostic techniques. In: Krachmer JH, Mannis MJ, Holland EJ, eds. Cornea. 2nd ed. Vol. 1 Philadelphia: Elsevier/Mosby; 2005:229-235. External Disease and Cornea, Section 8. Basic and Clinical Science Course, AAO, 2010.

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Neurotrophic Keratitis: Classification

Mackie classification

- *Stage I is characterized by hyperplasia and/or irregularity of the epithelium, evolving to punctate keratopathy, corneal edema, neovascularization, stromal scarring.*
- Stage II is defined by a recurrent or persistent epithelial defects or a PED without stromal thinning.
- Stage III: stromal involvement leads to corneal ulcer, melting and perforation

Mackie IA. Neuroparalytic keratitis. Current Ocular Therapy. Philadelphia, PA: WB Saunders; 1995:452-4.

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Endogenous nerve growth factor (NGF) and its role in NK:

Neurotrophic keratitis (NK) is a result from impaired trigeminal corneal innervation	Endogenous NGF maintains corneal integrity by three mechanisms
↓ Lacrimation and blink reflex ↓ Epithelial cell vitality, metabolism, mitosis ↓ Epithelial trophism and repair ↑ Stromal and intracellular edema ↓ *Microvilli* ↓ Development of the basal lamina	Cell proliferation Tear secretion Corneal reinnervation

Nerve damage ⇨ loss of corneal sensitivity ⇨ NK

Mastropasqua et al. (2017) J Cell Physiol 232:717-24

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Severity-Based Therapy

Stage	Therapy
1	• Preservative-free artificial tears formulations • Punctal occlusion • Hydrogel contact lens (consider large diameter) • Recombinant human NGF (rhNGF, cenegermin) • Serum/plasma/platelet rich plasma
2	Supportive therapies plus: • rhNGF • Scleral lens (± serum/plasma) • Amniotic membrane • Botulinum induced ptosis, Tarsorrhaphy
3	• rhNGF • Keratoplasty + scleral lens, tarsorrhaphy, neurotization

Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Ophthalmol*. 2014;8:571-579. Sheha H, Tighe S, Hashem O, Hayashida Y. Update on cenegermin eye drops in the treatment of neurotrophic keratitis. *Clin Ophthalmol*. 2019;13:1973-1980. Published Oct 7, 2019.

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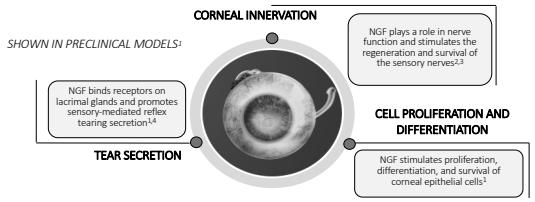
Endogenous NGF Maintains Corneal Integrity By Three Mechanisms

Endogenous nerve growth factor acts through specific high-affinity (ie, TrkA) and low-affinity (ie, p75NTR) nerve growth factor receptors in the anterior segment of the eye to support corneal innervation and integrity.[1]



1. Mastropasqua L, Massaro-Giordano G, Nubile M, Sacchetti M. Understanding the pathogenesis of neurotrophic keratitis: the role of corneal nerves. *J Cell Physiol*. 2017 Apr;232(4):717-724. 2. Müller LJ, Marfurt CF, Kruse F, Tervo TM. Corneal nerves: structure, contents and function. *Exp Eye Res*. 2003 May;76(5):521-42. 3. Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Ophthalmol*. 2014;8:571-9. 4. Muzi S, Colafrancesco V, Sornelli F, et al. Nerve Growth Factor in the Developing and Adult Lacrimal Glands of Rat With and Without Inherited Retinitis Pigmentosa. *Cornea*. 2010;29:1163–1168.

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Serum /Plasma Therapy

- **Serum/plasma have reported efficacy as primary or adjunct therapy**
  - Reported success of serum alone (20-50% concentration) ranges from 71 to 100% within 90 days (Guadilla et al. Arch Soc Esp Offalmol 2013; Jeng and Dupps Cornea 2009; Pflugfelder *AJO* 2006)
  - Umbilical cord serum may be more effective and has higher concentrations of substance P and NGF than peripheral blood serum (Yoon KC et al. *Ophthalmology* 2007)
  - Epithelial defect healed in 97.4% of stage 2-3 NK after 11 weeks of plasma rich in growth factors (PRGF) (Sanchez-Avila RM et al. *Int Ophthalmol* 2018)
  - Serum can be used safely in combination with SiH CL. No inflammation or CL deposits were observed (Choi JA *ECL* 2011)

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Amniotic Membrane

- Randomized clinical trial reported healing of refractory neurotrophic ulcers with conventional therapy (lubrication plus BCL or tarsorrhaphy) or amniotic membrane transplant (AMT). Healing rates were similar in the 2 groups: 67% with conventional therapy and 73% with AMT (Khokhar S et al. Cornea 2005)
- AMT was also equivalent to autologous serum (AS) in healing neurotropic ulcers: 70% for AS and 73% for AMT (Turkoglu E et al. Semin Ophthalmol 2014)
- Multilayer AMT recommended for deep ulcers and Descemetoceles (Kruse F et al. Ophthalmology 1999)

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Scleral Lenses

- Use of fluid filled scleral contact lenses for treatment of NK initially reported decades ago (Romero-Rangel et al. *AJO* 2000)
- Non-healing corneal epithelial defects with BCL healed without recurrence in all 9 eyes treated with PROSE scleral lens (Ling J et al. *Am J Ophthalmol* 2013)
- Overnight wear (with close monitoring) may accelerate healing (Lim P et al. *AJO* 2013)

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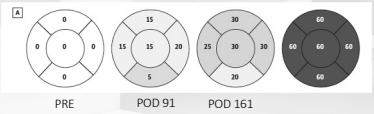
Corneal Neurotization

- Corneal sensitivity restored after sural nerve grafts (Elbaz et al. *JAMA Ophthalmol* 2014)
- Free sural nerve graft was coapted end-to-side with supratrochlear nerve and the distal portion of the nerve was separated into fascicles that were distributed around the limbus
- Corneal sensitivity, measured pre- and post-op with the Cochet-Bonnet esthesiometer, returned to normal after 5 months



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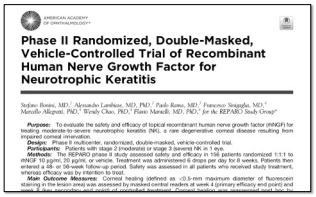
cenegermin-bkbj 20 mcg/ml was approved by FDA in August 2018



Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis

Stefano Bonini, MD,[1] Alessandro Lambiase, MD, PhD,[1] Paolo Rama, MD,[1] Francesco Sinagaglia, MD,[1] Marcello Allegretti, PhD,[2] Wendy Chao, PhD,[2] Flavio Mantelli, MD, PhD,[1] for the REPARO Study Group*

- Approved for the treatment of neurotrophic keratitis in adults and children age 2 and older
- Available for ordering since January 2019
- Available through specialty pharmacy

Bonini S, Lambiase A, Rama P *et al.* Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis. *Ophthalmology* 2018;125:1332–1343.

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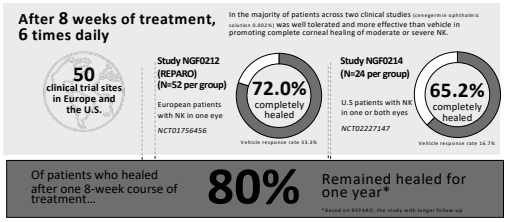
Study Conclusions

Up to 72% of patients achieved complete corneal healing;
80% of healed patients were recurrence free after 1 year*



1. Bonini S, Lambiase A, Rama P *et al. Ophthalmology* 2018;125:1332–1343.
2. Chao W, J. ADC, R. D *et al.* Data on file. Healing of persistent epithelial defects or corneal ulcers by recombinant human nerve growth factor eye drops in patients with stage 2 or 3 neurotrophic keratitis. Presented at: Congress of the European Society of Ophthalmology (SOE) 10–13 June, 2017, Barcelona, Spain. 2017.

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Treatment

- Continue:
  - Cyclosporine 0.05% BID OU
  - Heat Mask
- Stop
  - Oral ceterizine
- Order
  - Cenegermin 20 mcg/mL – Patient to call once meds come in to review meds / demo proper usage
  - Ceterizine ophth sol BID OU
- Follow Up
  - 3-4 months glaucoma / Dilate OCT - G

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Case Ex. Somebody Help Me

- NP 29 yowf presents for significant dry eyes. Eyes are always in pain, burning, gritty and feels like sand paper. Currently using serum tears 50% qid ou and would like to get serum tears 75%.
- Oc Hx: 8 years
- Med Hx: ADHD, Hypothyroid
- Meds: Nortriptyline, synthroid
- What questions do you want to ask?

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Previous Treatments

- Omegas – stopped on her own – NI
- Cyclosporine BID OU – stopped after 1 month / made eyes worse
- Prednisolone QID OU – stopped due to NI
- Plugs – 3 month plugs all puncta / NI
- Lifitegrast BID OU – stopped after 2 mos / made eyes worse
- Loteprednol 0.2% - NI
- Doxycycline 100 mg BID po – stopped after 2 weeks
- Erythromycin ung – NI
- Neomycin/polytrim/dexamethasone ung – NI
- Multiple preservative free drops

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Clinical Exam

- UCVA 20/20 OU
- You know what a normal eye looks like
- Any Other Tests??
- Diagnosis??

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Causes of NCP

- Trauma
- Chemical exposures
- Previous infection
- Eye surgery
- Systemic disease
  - Autoimmune or inflammatory conditions
  - Depression
  - Diabetes
  - Fibromyalgia
- Other neurological disease
  - Trigeminal neuralgia
  - Migraine

Moshirfar M, Benstead EE, Sorrentino PM, et al. Ocular Neuropathic Pain. [Updated 2022 Aug 22]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-.

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Diagnosis of NCP

- No universal criteria for dx
- Case history
- Initial triggers for pain
- Time course
- Alleviating and exacerbating factors
- Treatment history
- Symptoms - Topical lubricants provide no / minimal relief
- Clinical Exam
  - Pain without stain
  - Topical anesthetic relief
- Confocal Microscopy

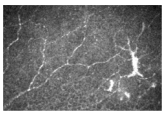

Photo Courtesy of Scott Hauswirth, OD

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Neuropathic Pain

- Treatment to either:
  - Regenerate nerves
  - Reduce inflammation that makes nerves more sensitive
- Treatment Options
  - Serum tears
  - Steroids
  - Amniotic membrane
  - Neurostimulation
  - Blue filter glasses
  - Systemic neuro-modulatory therapies
  - Biologics

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Autologous Serum

- Blood drawn via 18 gauge needle – 40 mL blood collected into blood tubes
- Blood set aside to clot at room temperature for two hours, then centrifuged at 5600 rpm for 10 minutes
- Serum filtered to remove fibrin strands before mixing with saline
- Typically start with 20% up to 50%
- Unopened bottles stored in freezer up to 3 months; open bottles in refrigerator for 48 hours
  - Potential for safe refrigerator storage for up to 1 month

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Healing factors in Autologous Serum

- Vitamin A
- Lysozyme
- Transforming Growth Factor-beta (limits epithelial healing)
- Fibronectin
- Substance P
- Insulin-like growth factor-1
- Nerve growth factor

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Benefits and Pitfalls of Autologous Serum

Benefits
- Preservative free and innately allergy free
- Adverse events rare
- Improvement in symptomology
- Demonstrated improvement in staining (Tsubota – SS pts)

Complications
- Cost – no insurance coverage
- Frequent blood draw
- Availability of labs to make ASED
- Strict handling

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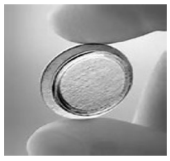
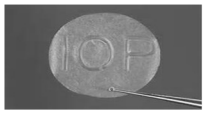
Amniotic Membranes and Amniotic Membrane Extract Eye Drop (AMEED)



Cryopreserved Membranes



Dry Membranes

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Pros and Cons of Amniotic Membrane Modalities

Cryopreserved
- Self-retaining on cornea
- Higher levels of regenerative complex HC-HA/PTX3
- Shorter storage life – requires refrigeration
- Potential discomfort from symblepharon ring
  - Avoid with filtering procedures

Dehydrated
- Longer storage life – room temperature
- No ring = better comfort
- Frequent slippage
- Requires bandage lens to maintain position

***For all amniotic membranes, RCTs limited**

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Hindawi
Journal of Ophthalmology
Volume 2017, Article ID 6404918, 10 pages
https://doi.org/10.1155/2017/6404918

Hindawi

Clinical Study

Corneal Nerve Regeneration after Self-Retained Cryopreserved Amniotic Membrane in Dry Eye Disease

Thomas John,[1,2] Sean Tighe,[3,4] Hosam Sheha,[3,4,5] Pedram Hamrah,[6,7] Zeina M. Salem,[6,7] Anny M. S. Cheng,[3,4] Ming X. Wang,[8] and Nathan D. Rock[8]

[1]*Thomas John Vision Institute, Tinley Park, Cook County, IL, USA*
[2]*Loyola University at Chicago, Maywood, Chicago, IL, USA*
[3]*Ocular Surface Center and TissueTech, Inc., Miami, FL, USA*
[4]*Florida International University Herbert Wertheim College of Medicine, Miami, FL, USA*
[5]*Research Institute of Ophthalmology, Cairo, Egypt*
[6]*Boston Image Reading Center, Tufts Medical Center, Tufts University School of Medicine, Boston, MA, USA*
[7]*Center for Translational Ocular Immunology, Department of Ophthalmology, Tufts Medical Center, Tufts University School of Medicine, Boston, MA, USA*
[8]*Wang Vision Institute, Nashville, TN, USA*

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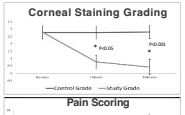
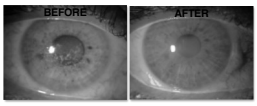
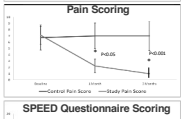
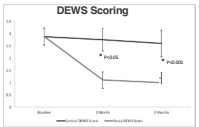
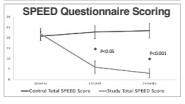
Improvements in Clinical Signs and Symptoms











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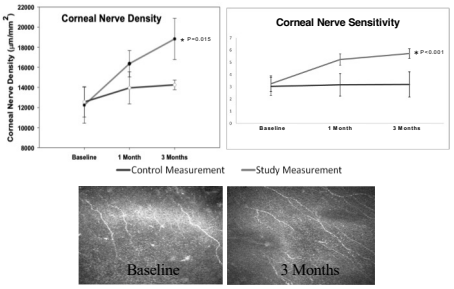
Improvements in Corneal Nerve Density & Sensitivity



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Dry Eye Disease

- Anakinra (Kineret)
  - Recombinant version of human IL-1Ra currently approved for RA
  - Inhibits the interaction of IL-alpha and IL-beta
  - IL-1 directly correlated to corneal fluorescein staining, nociception
  - Anakinra 2.5% topical
    - Significantly more effective than vehicle in improving signs and symptoms of dry eye
    - 4x reduction in corneal staining
    - 6x reduction in symptoms
    - Termination of use at week 12 led to increased symptoms at 1 month

Amparo et al. **Topical interleukin 1 receptor antagonist for treatment of dry eye disease: a randomized clinical trial.** JAMA Ophthalmol. 2013 Jun;131(6):715-723. doi: 10.1001/jamaophthalmol.2013.195.

44

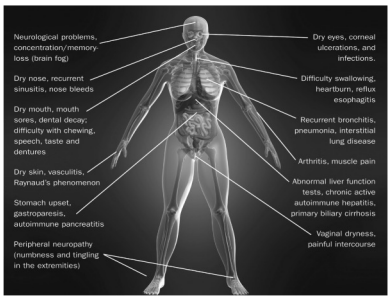
Rituximab (Rituxan)

- A monoclonal antibody that targets human CD20 on B-cells
- B-cell depletion postulated via:
  - Complement-dependent cytotoxicity
  - Antibody-dependent cell mediated cytotoxicity
  - Triggers apoptosis
- Two Large, multi-centered, double blind, RCTs (TEARS, TRACTISS)
  - 1g rituximab intravenously vs. placebo
  - No statistical significance on the endpoints of ocular dryness and Schirmer I in both studies

1. Brown S, Navarro Coy N, Pitzalis C, Emery P, Pavitt S, Gray J, Hulme C, Hall F, Busch R, Smith P, et al. The TRACTISS protocol: a randomised double blind placebo controlled clinical trial of anti-B-cell therapy in patient primary Sjogren's syndrome. BMC Musculoskelet Disord. 2014;15:21. doi: 10.1186/1471-2474-15-21.
2. Devauchelle-Pensec V, Mariette X, Jousse-Joulin S, Berthelot JM, Perdriger A, Hachulla E, Puéchal X, Le Guern V, Sibilia J, Gottenberg JE, et al. OP0065 tolerance and efficacy of rituximab in primary sjogren syndrome (TEARS): results of a randomized controlled trial. Ann Rheum Dis. 2014;73(Suppl 3):75.71–75.75.
3. Brown S, Navarro Coy N, Pitzalis C, Emery P, Pavitt S, Gray J, Hulme C, Hall F, Busch R, Smith P, et al. Treatment of primary SjÖgren syndrome with rituximab a randomized trial. Ann Intern Med. 2014;160(4):233–242.

45

Sjögren's Is More than Dry Eye[1]



Depression 3 x more likely

Lymphoma 5% of SS

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Guidelines for use of Biological Medications in Sjogren's Disease

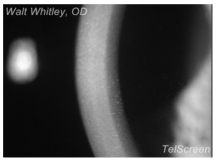
- TNF-a inhibitors should not be used to treat sicca symptoms in patients with primary SD.
  - Strength of recommendation: strong
- Rituximab may be considered as a therapeutic option for KCS in patients with primary SD and for whom conventional therapies, including topical moisturizers, secretagogues, anti-inflammatories, immunomodulators, and punctual occlusion, have proven insufficient.
  - Strength of recommendation: weak due to inclusion criteria

Verstappen G et al. The value of rituximab treatment in primary Sjögren's Sydrome. Clin Immunol. 2017 Sep;182:62-71.

47

"The Common Eyeritis"

- 32YOWM, Red, Painful Eye OD, Photophobic, No discharge
- No previous episodes
- Ocular/Medical Hx: Unremarkable
- No other associated symptoms
- SLE: 2+ injection / 2+ cells



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Common Eyeritis

- Once considered a single disease entity, we now know can be caused by autoimmune disease, infection, malignancy, and exposure to toxins
- Inflammation of the iris, ciliary body or choroid / combination of these
- 87.6% anterior / 55% idiopathic / 21% traumatic / 25% have an underlying cause
- Tx may include systemic workup and/or systemic meds
- The sight-threatening complications of uveitis include glaucoma, damage to the retina, and macular edema.

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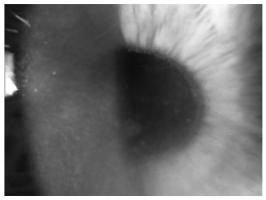
Anterior Uveitis

- Causes
  - Idiopathic
  - Traumatic
  - HLA-B27
  - Herpetic
- Can be recurrent, recalcitrant, granulomatous, or non-granulomatous



Retrieved from http://www.oculist.net/downaton502/prof/ebook/duanes/pages/v4/v4c031.html

50

Intermediate Uveitis

- 8-15% of all uveitis
- Involves pars plana, peripheral retina, vitreous
- Anterior vitreous cells
  - Scleral depression
  - B scan
- Associated conditions
  - MS
  - Sarcoid
  - Syphilis

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Posterior Uveitis

- Common findings
  - Active inflammation
  - Scarring
  - Vasculitis
- Consider infectious causes

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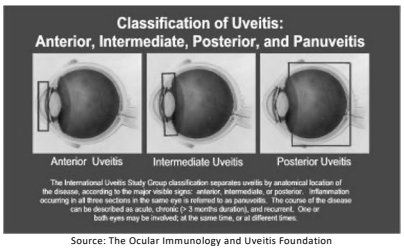
Panuveitis



Source: The Ocular Immunology and Uveitis Foundation

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Condition	Clinical Features	Test Indicated
Ankylosing spondylitis	Young male, low back pain, chest pain	HLA-B27, sacroiliac X-ray
Reiter's syndrome	Young male, arthritis, urethritis, conjunctivitis	HLA-B27, ESR, CRP
Juvenile idiopathic arthritis	Slight male predilection, sacroiliitis common	ANA, RF, knee radiograph
Inflammatory bowel disease	Ulcerative colitis, diarrhea, abdominal cramps	HLA-B27, GI referral for endoscopy
Sarcoidosis	African Americans, females, vasculitis, vitritis	ACE, chest X-ray or CT scan
Tuberculosis	Prolonged cough, fever, chills, night sweats, weight loss	PPD, chest X-ray
Syphilis	Hx of sexual contact with infected person, rash, fever, malaise, headache, joint pain	FTA-ABS, VDRL, RPR
Toxoplasmosis	Immunocompromised status, exposure to cats, hx of eating raw meat, punched-out retinal lesions	Toxoplasma IgG or IgM for acute acquired cases
Lyme disease	Recent tick bite	Lyme Western Blot

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When Should Lab Tests Be Ordered?

- Bilateral cases
- Atypical age group
- Recurrent uveitis
- Recalcitrant cases
- Hyperacute cases
- Worsens with tapering
- VA worsens
- Immunosuppressed

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Treatments for Uveitis

- Steroids
  - Topical
  - Local
  - Systemic
- NSAIDs
- Cycloplegics
- Analgesics
- Immunosuppressants
- Calcineurin inhibitors
- Biological blockers
- Glaucoma medications

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Steroid Pulse Therapy

- QID to Q 1 Hour for 7 to 10 Days
- Zero Tolerance for AC Cells
- Avoids Surface Toxicity
- Quick & Dirty
- Hit It Hard and Fast: Aggressive
- **Treat and Follow**

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Systemic Therapy for Inflammatory Disease

- Acute inflammatory episodes typically necessitate steroid treatment (topical, periocular, intraocular, systemic)
- Steroids exhibit great efficacy (especially in anterior uveitis), but come with significant side effects, limiting chronic use
- MUST Study
  - Local and implant steroids effective for uveitis treatment
  - High incidence of local ocular SE and systemic complications

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Considerations for Steroid Sparing Options

- Steroid duration
  - Duration over 3 months
  - Unable to taper below 10mg po prednisone
- Relapse or recurrence
  - 3 - 4 recurrences or more
- Severity of local/Systemic Complications

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Disease Modifying Anti-rheumatic Drugs (DMARDs)

- Traditional – restrict immune system broadly
  - Antimetabolites – methotrexate, mycophenolate mofetil
  - T-cell inhibitors – cyclosporine, tacrolimus
  - Alkylating agents – cyclophosphamide, chlorambucil
  - Antimalarials - hydroxychloroquine
- Targeted – block precise pathways in immune cells
  - PDE4 Inhibitor – Apremilast / Otezla
  - Janus Kinase Inhibitor – Tofacitinib / Xeljanz
- Biologics work by targeting specific steps in the inflammatory process and next "steps"

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Antimalarials - hydroxychloroquine sulfate

- Indicated for the treatment of discoid and systemic lupus erythematosus, rheumatoid arthritis, and malaria
- Dosage: 200mg to 400mg per day
- Primary risk factors
  - Duration > 5 years
  - Cumulative dose >1000g
  - Age
  - Systemic – High BMI, liver, kidney dysfunction
  - Ocular – retina or macular changes

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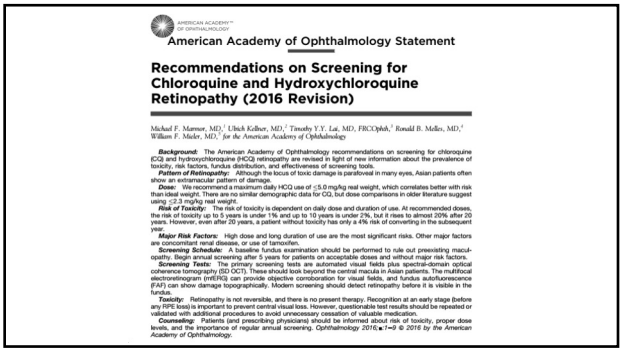

American Academy of Ophthalmology Statement

Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy (2016 Revision)

Michael F. Marmor, MD,[1] Ulrich Kellner, MD,[2] Timothy Y.Y. Lai, MD, FRCOphth,[3] Ronald B. Melles, MD,[4] William F. Mieler, MD,[5] *for the American Academy of Ophthalmology*

Background: The American Academy of Ophthalmology recommendations on screening for chloroquine (CQ) and hydroxychloroquine (HCQ) retinopathy are revised in light of new information about the prevalence of toxicity, risk factors, fundus distribution, and effectiveness of screening tools.

Pattern of Retinopathy: Although the locus of toxic damage is parafoveal in many eyes, Asian patients often show an extramacular pattern of damage.

Dose: We recommend a maximum daily HCQ use of ≤5.0 mg/kg real weight, which correlates better with risk than ideal weight. There are no similar demographic data for CQ, but dose comparisons in older literature suggest using ≤2.3 mg/kg real weight.

Risk of Toxicity: The risk of toxicity is dependent on daily dose and duration of use. At recommended doses, the risk of toxicity up to 5 years is under 1% and up to 10 years is under 2%, but it rises to almost 20% after 20 years. However, even after 20 years, a patient without toxicity has only a 4% risk of converting in the subsequent year.

Major Risk Factors: High dose and long duration of use are the most significant risks. Other major factors are concomitant renal disease, or use of tamoxifen.

Screening Schedule: A baseline fundus examination should be performed to rule out preexisting maculopathy. Begin annual screening after 5 years for patients on acceptable doses and without major risk factors.

Screening Tests: The primary screening tests are automated visual fields plus spectral-domain optical coherence tomography (SD OCT). These should look beyond the central macula in Asian patients. The multifocal electroretinogram (mfERG) can provide objective corroboration for visual fields, and fundus autofluorescence (FAF) can show damage topographically. Modern screening should detect retinopathy before it is visible in the fundus.

Toxicity: Retinopathy is not reversible, and there is no present therapy. Recognition at an early stage (before any RPE loss) is important to prevent central visual loss. However, questionable test results should be repeated or validated with additional procedures to avoid unnecessary cessation of valuable medication.

Counseling: Patients (and prescribing physicians) should be informed about risk of toxicity, proper dose levels, and the importance of regular annual screening. *Ophthalmology 2016;■:1–9 © 2016 by the American Academy of Ophthalmology.*

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Antimetabolites

- Methotrexate - a folic acid analog and dihydrofolate reductase inhibitor
  - Indications - Acute lymphoblastic leukemia, Trophoblastic neoplasms, Lung cancer, Psoriasis, RA
  - MOA - Inhibits DNA synthesis, repair and cellular replication
  - Dosage
    - Usually 7.5 to 25 mg/week orally
    - Occasionally subcutaneously delivered to reduce side effects
  - Onset – 2-12 weeks
  - Side effects
    - Gastrointestinal disturbance, hepatotoxicity, oral ulcers, fatigue, alopecia, bone marrow suppression, pneumonitis, fetal loss, and infections
  - Comanage with rheumatology

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Traditional DMARDs - T-Cell Inhibitors

- Cyclosporine
  - Indications
    - Organ transplant
    - RA
    - Psoriasis
  - MOA - Inhibits T-cell activation
  - Dosage - 2.5–10 mg/kg/day PO twice daily
  - Onset - 2–6 weeks
  - Side effects
    - Nephrotoxicity, hypertension, hirsutism, gingival hyperplasia, and infections
  - Comanaged with rheumatology or nephrologist

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Alkylating Agents

- Cyclophosphamide
  - Indication
    - Lymphoma
    - Myeloma
    - Leukemia
  - MOA – nonspecific alkylating agent that alters the composition of DNA bases
  - Dosage - 1–3 mg/kg/day PO
  - Onset – 2-8 weeks
  - Overall, approximately 76% gained sustained control of inflammation (for at least 28 days) within 12 months
  - Side effects
    - Bone marrow suppression, infections, hemorrhagic cystitis, increased risk of malignancy, sterility, and alopecia
  - Comanaged with rheumatologist + reproductive medicine specialist

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Biologics Therapies

- Originally considered 2-3rd line agents

- Considerations
  - 1st line (following steroid pulse) to control active inflammation
  - When conventional immunosuppressants fail to control uveitis
  - More targeted approach
  - Safety profile

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Biologic Therapies in Noninfectious Uveitis

- Suppress inflammation with oral steroid while starting biologic
  - Taper PO steroids 4-6 weeks
  - Needs 4-6 weeks onset of action
- Rule out systemic conditions
  - Infections (TB and Hepatitis)
  - Multiple sclerosis
  - Risk of heart failure development
  - Coordinate care with specialist

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Common Systemic Biologics in Inflammatory Disease

- Tumor Necrosis Factor (TNF-alpha) Inhibitors
  - Humira (adalimumab)***
  - Remicade (infliximab)
  - Enbrel (etanercept)
- Lymphocyte Inhibitors
  - Rituxan (rituximab)
  - Orencia (abatacept)
- Interferons
- Anti-Interleukin antibodies
  - Actemra (toclizumab)***

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Tumor Necrosis Factor

- TNF found in two forms in the body
  - Transmembrane – maintain innate immune response and tolerance to autoantigens
    - Inhibition results in increased sensitivity to infection, exacerbation of demyelinating conditions
  - Soluble – drives inflammatory response
    - Inhibition leads to anti-inflammatory effect
- Current TNF alpha inhibitors act on both forms

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TNF-Alpha Inhibitors

- Adalimumab (Humira)**
  - Only FDA approved biologic for treatment of intermediate, posterior, or panuveitis
  - Subcutaneous injection
- Infliximab (Remicade)**
  - IV infusion
- Etanercept (Enbrel)
  - Not shown to benefit ocular disease

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TNF-Alpha Inhibitors

- Infliximab particularly effective in Behcet's
  - 86% remission rate in as little as two weeks with infliximab alone for PU
  - Also effective in JIA and birdshot chorioretinopathy
  - Chief application is for those who have failed adalimumab
- Adalimumab very effective in uveitis control
  - VISUAL 1 and 2 – reduction in treatment failure and relapse rate
  - SYCAMORE – trial halted before conclusion, clear benefit of adalimumab plus methotrexate versus methotrexate alone in JIA

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Adverse Effects with TNF-a Inhibitors

- Activation of latent TB or hepatitis
- Demyelinating disease
  - These first two tied with action on tmTNF
  - Must rule out MS with MRI in patients with pars planitis
- Hepatotoxicity
- Secondary malignancies
- Drug-induce disease
- Tachyphylaxis – due to antibody development
- **MULTISPECIALTY APPROACH TO MANAGEMENT IS CRITICAL**

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Interferons

- Naturally occurring cytokines which aid in regulation of immune system
  - Anti-proliferation of T cells
- Subcutaneous injections
- IFN-alpha2a
  - Effective in Behcet's – 94% reach complete or partial remission
  - Small cohort of intermediate uveitis or MS related uveitis showed significant reduction in macular edema with improved VA
- Side effects
  - Flu-like symptoms
  - Depression

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Anti-Interleukins

- Toclizumab (Actemra)
  - IL-6 antagonist, used in moderate to severe RA, GCA, PJIA, SJIA
  - Subcutaneous or IV infusion
  - STOP-Uveitis study – reduction of vitreous haze and CME at either 4 or 8 mg/kg of IV infusion
    - Mean 44% decrease in VH
    - CMT – 83.88 um
  - Recently approved for treatment of GCA
    - Subcutaneous injection weekly or every other week with concurrent steroid taper showed superior remission to steroid treatment alone
    - 53-56% remission versus 14% placebo
    - Dosed at one subcutaneous injection weekly

74

Acthar Gel (repository corticotropin injection)

- Indicated for severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as: keratitis, iritis, iridocyclitis, diffuse posterior uveitis and choroiditis, optic neuritis, chorioretinitis, anterior segment inflammation
- Complex formulation containing ACTH, a melanocortin peptide that binds to the 5 identified melanocortin receptors (MCRs) on tissues and cells throughout the body
- MOA unknown however in addition to stimulation of the body's endogenous cortisol release, Acthar is believed to impact steroid-independent immunomodulatory and anti-inflammatory pathways
- Currently no clinical trial data available for uveitis

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Biologics: Side Effects

- Increased risk of infection
- Reactivate Hepatitis B
- Allergic reaction
- Symptoms
  - IV infusions - Shortness of breath, chills, redness, itchiness, itchy eyes, itchy lips
  - Injections – redness, itchiness, warm/tender to touch, full body rash
- Less common
  - CNS disorders
  - Cardiac issues
  - Lupus-like syndrome

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Botulinum Toxin

- Cosmetic uses
- Functional uses
  - Blepharospasm – 70-90% effective
  - Hemifacial spasm
  - Eyelid apraxia
  - Myokemia
  - Lid Retraction
    - Exposure keratopathy
  - Strabismus

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Botulinum Toxin

- Neurotoxin produced by *C. botulinum*
- Blocks release of acetylcholine from presynaptic neuron at neuromuscular junction causing paralysis
- Serotype A used commercially in two forms:
  - onabotulinumtoxinA
  - abobotulinumtoxinA

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Botulinum Toxin

- Inhibits neurotransmission at neuro-muscular junction (acetylcholine, others)
- Leads to chemical denervation striated muscle
- Peaks at 2 weeks
- Neuronal sprouting heralds return of function @ 3 – 6 mos.

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Botulinum Toxin

- On-label therapeutic uses in ophthalmology
  - Blepharospasm
  - Hemi-facial spasms
  - Strabismus
- Off-label therapeutic uses in ophthalmology
  - Protective ptosis → induce upper lid ptosis and closure
    - Lag ophthalmos s/p acute Bell's Palsy, exposure keratopathy, poorly healing defect
  - Alternative to permanent tarsorrhaphy
  - Tx of filamentary keratitis with a blepharospasm component

80

Case Of The Red Irritated Swollen Eye

- 50 yo female with 4 week history of redness irritated tearing eyes
- Otherwise healthy hasn't ever seen an eye doctor

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……..or perhaps she has seen 6 other doctors

- 55yo F dx as chronic conjunctivitis with a 3 month history or red eyes and tearing after trials of :
- Artificial tears
- Antibiotic drops
- Steroid drops
- Antibiotic steroid combination drops
- Stopping all drops
- Ointments
- Lid scrubs
- Hot compresses
- Cold compresses
- Luke warm camomile tea and honey compresses
- Acupuncture, acupressure, meditation

if its red consider TED

82

Teprotumumab (RV 001)

- An antibody directed against IGF-1, the growth factor pathway associated with the thyroid-hormone receptor
- Teprotumumab is the only medicine to date proven to reduce overall clinical severity and proptosis, and provide a sustained response.[1]
- Can halt progression of active disease and reverse any changes associated with TED, and the effects are long-lasting.

Primary endpoint: 2mm reduction in proptosis - 82.9% vs. 9.5%

N = 87

1. Smith TJ, Kahaly GJ, Ezra DG, et al. Teprotumumab for thyroid-associated ophthalmopathy. N Engl J Med 2017;376:18:1748-61.

83

Other Biologics for TED

- Rituximab
  - Two large, randomized, controlled, concurrent trials were conducted: one in Europe and one in the United States
  - Unfortunately, the results were conflicting, with the European study suggesting a beneficial effect of rituximab[6] and the United States study showing no improvement
- Tocilizumab (Actemra, Genentech)
  - Case reports of improvement in TED
  - Recently completed a randomized, controlled trial, the results of which are pending.

84

Treatment Options

Non-nAMD
- Observation
- Antioxidants/ AREDS 2

nAMD
- Antioxidants/ AREDS 2
- Anti-VEGF agents:
  - Ranibizumab 0.5 mg
  - Bevacizumab 1.25 mg
  - Aflibercept 2.0 mg
  - Brolucizumab 6.0 mg
  - Faricimab 6.0 mg
  - Port Delivery System

DME
- Focal laser
- Anti-VEGF agents:
  - Ranibizumab 0.5 mg
  - Bevacizumab 1.25 mg
  - Aflibercept 2.0 mg
  - Brolucizumab 6.0 mg
  - Faricimab 6.0 mg
- Intravitreal steroids
- Vitrectomy

85

Anti-VEGF

- Bevacizumab
  - Full length monoclonal antibody that non-specifically binds to VEGF at two sites
  - Off-label use, must be compounded
  - CHEAPER
- Ranibizumab
  - Fragment antigen binding monoclonal antibody derived from bevacizumab
  - Specifically targets VEGF-A
  - 0.3 and 0.5 mg injection

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Anti-VEGF

- Aflibercept
  - Fully humanized recombinant protein -- VEGFR-1 and -2 binding sequences on antibody backbone
  - Binds VEGF-A, VEGF-B, and PlGF
    - Greater binding affinity
  - Less frequent dosing – 8 weeks after 3 monthly injection lead in

87

Systemic Considerations in Anti-VEGF

- True prevalence of AE's difficult as patients often have multiple co-morbidities
- Systemic effects uncommon, but include the following:
  - Stroke
  - Hypertension
  - Myocardial infarction
  - Hemorrhage
  - Decreased pulmonary surfactant – pediatric consideration

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Future Treatments in Pipeline

Newer Anti Vegf's -
- Brolucizumab
- Faricimab
- Abicipar
- Conbercept

Other Modalities -
Sustained release devices
Gene therapy
Stem cells

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Conclusions

- Biologics are the next wave of pharmaceutical development, and are playing an increasing role in the management of ophthalmic conditions
- Integration and management of these medications requires a multi-disciplinary approach
- Staying up to date on the most active biologics allows us to find a role in this care team

90